Medical Progress

Current Status of Renal Transplantation

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The success rate of renal transplantation has improved considerably during the past decade, with substantial improvements in both graft and patient survival. The quality of graft function, however, and not graft survival alone is increasingly determining the standards by which transplantation outcome is being judged. As the demand for kidney transplants continues to rise and transplants are being offered to an ever-increasing number of patients, organs are being sought from new supply pools and efforts are being made to use current resources more efficiently. Improvements in clinical management have allowed short-term complications such as infection and rejection to be better prevented or better diagnosed and treated. Fundamental advances in the understanding of the immunologic processes underlying both allograft rejection and acceptance and the introduction of new immunosuppressive agents have allowed a better use of drug therapy and have moved the goal of acquired transplant tolerance closer to attainment. With improved initial transplant success rates, the long-term transplantation outcome is becoming more important. The role of tissue matching in preventing chronic rejection is becoming more appreciated, and the long-term risks of malignancy, arteriosclerosis, and chronic rejection are being better recognized and managed.

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In the 1980s the success rate of cadaver-donor renal transplantation improved from one-year graft survival rates of around 50% to rates of 75% to 85%. At the same time, patient survival rates also improved, with one-year patient survival generally greater than 95%.[1-3] During the past decade, there have been parallel improvements in the detailed understanding of the fundamental processes causing rejection.[4,5] In clinical transplantation, improvements have been made in tissue typing, immunosuppression, and patient care and in the management of rejection, the diagnosis and treatment of acute and chronic allograft dysfunction, and the diagnosis and treatment of immunosuppression-related problems such as malignancy and infection.

Despite the continued relative shortage of cadaveric donor kidneys, renal transplantation grafting rates are progressively rising. The number of kidney transplants is increasing as groups of patients previously denied them—including those sensitized to HLA antigens,[6] the elderly,[7-9] the very young,[10] and high-risk patients[11]—receive kidneys.

The solution to the shortage of kidneys lies first with the optimal use of currently available cadaver kidneys and, second, in harvesting grafts from new patient pools, such as kidneys from pediatric and elderly donors[12-14] and from living-related and unrelated donors.[15-17]

Pretransplantation Measures to Improve Graft Survival

Tissue Typing

The most important transplantation antigens in humans and animal models are determined by a polymorphic group of genes, the major histocompatibility complex (MHC), which in humans are called human leukocyte antigens. The protein products of these genes are present on most cell surfaces and fall into two important classes: the HLA class I antigens (including HLA-A, -B, and -C) and the HLA class II antigens (including the HLA-DR, -DP, -DQ, and other D-related antigens). A set, or haplotype, of these antigens is inherited from each parent and is codominantly expressed. The resolution of the x-ray crystallographic structure of HLA-A2 has shown that the normal function of HLA molecules is to present antigen, in the form of a short peptide (5 to 22 amino acids), in the groove formed on the external surface of the molecules.[18] T-cell receptors recognize only antigen presented by this complex of MHC and antigenic peptide, and specialized antigen-presenting cells provide activation signals to T cells. This antigen presentation system is designed to trigger the immune system against viral and other intracellular pathogens and tumors. In transplantation, a situation unforeseen by nature, these same mechanisms result in the activation of effector cells such as T and B cells against the foreign MHC on the cells of the allograft, and the end result is rejection.

The stimulus activating the responding immune system to induce rejection, the major cause of allograft loss, depends on the number and type of HLA mismatches between recipient and donor. The most important HLA antigen mismatches driving the rejection response have been found to be the HLA-DR and HLA-B antigens, which are also the most polymorphic.[19] The benefits of HLA matching are best manifested in grafts between relatives, where matching between donor and recipient influences both short-term and long-term allograft survival.[16]

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ABBREVIATIONS USED IN TEXT
ALG = antilymphocyte globulin
CMV = cytomegalovirus
HIV = human immunodeficiency virus
IL-2 = interleukin 2
MHC = major histocompatibility complex

With the use of potent immunosuppressive protocols, early graft losses due to rejection can be suppressed, allowing the successful short-term function of even completely mismatched kidneys.[17,20] With longer follow-up, however, HLA disparity may contribute substantially to the loss of grafts with chronic rejection despite immunosuppression.[21,22] The rejection of poorly matched grafts results in a high incidence of sensitization, which can jeopardize the chances and success of subsequent transplantation and can result in a high mortality rate among patients returning to dialysis.[23] The success of second transplants may depend even more on HLA matching than does that of primary grafts.[24]

The need to establish the optimal use of a limited donor resource has led to a promotion of kidney sharing on a regional basis, with the aim of increasing the number of patients receiving well-matched grafts.[25-27] The national United Network of Organ Sharing program was set up with that aim. By current estimates an effective organ-sharing scheme could result in as many as 20% of patients being allocated A-, B-, and DR-compatible kidneys and in the number of patients receiving poorly matched kidneys being substantially reduced.[28] Organ-sharing programs may also have the benefit of reducing the number of highly sensitized patients awaiting second transplants. Nevertheless, kidney sharing is a contentious issue.[29,30] Some groups maintain that matching confers no benefit in cadaver or even living-related transplants[20] and that the longer storage required for exchanged kidneys causes damage that counterbalances any advantages of tissue-matched exchanged kidneys.[31] There has been progressive improvement, however, in the cold storage preservation of cadaveric kidneys, particularly with the introduction of the University of Wisconsin solution.[32-35] Still, it may require the application of exchange incentives to improve cooperation to produce an effective allograft exchange program.[36]

Lymphocytotoxic Antibody Crossmatch

After excluding ABO blood group incompatibility, testing for lymphocytotoxic antibodies against HLA class I and class II constitutes one of the most important matching procedures before transplantation. Such antibodies arise as a consequence of blood transfusion, pregnancy, and a previous transplant rejection.[37] The presence of antibody reacting with donor lymphocytes is excluded before transplantation, as such antibody has been associated with hyperacute and accelerated rejection.[38] Transplantation generally does not take place if deleterious lymphocytotoxic antibodies are detected in the crossmatch test before the procedure.[39]

Numerous controversies remain unresolved regarding the techniques and criteria of such testing,[40] including the relative value of historic and current antidonor crossmatches, the merits of anti-T- and anti-B-cell crossmatches,[41] the relative importance of sensitive assays such as fluorescence-activated cell sorting,[42-44] and the use of antiglobulin reagent in the cytotoxic crossmatch.[45] The crossmatch test does not identify antibodies against organ-specific antigens that are not expressed on donor lymphocytes.[46] Such antibodies may be found in the serum or allograft of a recipient[47] and may also play an important role in rejection processes.[48]

An increasing number of patients awaiting transplantation show a high degree of sensitization, which makes it difficult to find a compatible donor. This trend is exacerbated by the number of patients awaiting second transplants after the rejection of poorly matched first grafts. Many efforts to reduce the incidence of such presensitization have been ineffective,[49] but grafts bearing maternal HLA antigens may be useful in such sensitized recipients.[50] Highly sensitized patients do best when receiving transplants using well-matched grafts,[24] but such patients have also had successful transplants without regard to HLA matching.[51] Attempts have been made to reverse the sensitized state by plasmapheresis, antibody adsorption, and cyclophosphamide therapy, but these are still experimental.[52,53] Similar protocols have been used to remove hemagglutinins in recipients of ABO-incompatible grafts.

Blood Transfusion

In 1973 Opelz and co-workers noted a beneficial effect of random blood transfusion on the outcome of transplantation,[54] and this was subsequently confirmed by many groups. The recognition of the therapeutic benefits of random transfusion was followed shortly by the introduction of donor-specific blood transfusions in a subset of living-related transplant recipients.[55] Both random and donor-specific blood transfusions have been associated with a significant incidence of sensitization,[56] which can preclude subsequent transplantation. It has been postulated that donor-specific transfusion results in directly sensitizing recipients, whose reactive immune cells are then depleted by heavy immunosuppression soon after the transplantation.[57]

The role of blood transfusion as an adjunct to transplantation is now in question,[58] and the risk of sensitization and of the transmission of viral and other pathogens—particularly the human immunodeficiency virus (HIV)—must be weighed against the potential benefits. Further, with the introduction of recombinant erythropoietin,[59] the need to transfuse dialysis patients for anemia will be largely eliminated. If transfusion is required, however, using HLA-matched transfusions may reduce sensitization.[60] Recent data in the International Collaborative Transplant Study have led Opelz to suggest that there is now no compelling reason to undertake either random or donor-specific transfusion.[61]

Immunosuppressive Protocols

Immunosuppressive agents commonly used include azathioprine, prednisone, cyclosporine, antilymphocyte globulin (ALG) preparations, anti-CD3 monoclonal antibody (Orthoclone OKT3), ionizing irradiation,[62] and alkylating agents such as cyclophosphamide.[63] Azathioprine and prednisone were the mainstay of therapy in the 1960s and 1970s, and antilymphocyte globulin was added in the late 1960s. Cyclosporine became available in the 1980s and is now central to most protocols.

The introduction of cyclosporine has been associated with a period of progressive improvement in the success of renal transplantation,[64] which has also been translated into an improvement in quality of life for patients.[65,66] The mechanisms

of its actions are still being investigated, but it effectively inhibits the release of cytokines, especially interleukin 2 (IL-2), known to be important in the generation of the rejection response.[67-69] The main side effect of cyclosporine is, paradoxically, nephrotoxicity.

Cyclosporine was initially used alone or with prednisone, but to minimize side effects, particularly nephrotoxicity that occurs at high dosage, there has been a trend toward combining agents at a lower dosage to achieve additive or synergistic effects.[70] The rationale of multiple-agent protocols is that each immunosuppressive acts at different sites in the immune system. By using lower doses of each agent, it is hoped that the side effects of higher doses will be avoided while the benefits of each agent are retained. Triple-drug therapy with azathioprine, prednisone, and cyclosporine has become widely used, as has quadruple-drug therapy, with ALG induction followed by triple-drug therapy.[70] Despite the general tendency to use multiple agents, some transplant centers continue to use one- or two-drug protocols with comparable graft survival rates.[71,72] The combination of cyclosporine and azathioprine as maintenance therapy can avoid the long-term use of steroids.[73,74]

The main factor driving the trend toward multiple-drug therapy is the nephrotoxicity of cyclosporine, the use of which can increase the duration of early nonfunction of a transplanted kidney.[75] To minimize early nonfunction, some protocols include low doses of cyclosporine whereas others avoid the early use of cyclosporine by using ALG, azathioprine, and prednisone followed by cyclosporine only after adequate renal function occurs.[70]

Combination immunosuppression still does not completely prevent rejection episodes or graft loss, especially in second transplants or in patients who do not have good tissue matching.[3,76] Combined therapy may also be associated with a substantial risk of patient morbidity from opportunistic infection[77] or a malignant lesion such as lymphoma.[78] For this reason prophylactic broad-spectrum antibiotics and acyclovir may be used to prevent infection.[79] Monitoring cyclosporine levels in whole blood, serum, or plasma to adjust the dosage is widely done to minimize the side effects of using cyclosporine.[80-83] Because of nephrotoxicity, cost, and the unknown effects of long-term cyclosporine use, some centers have begun converting from cyclosporine to conventional azathioprine and prednisone therapy.[84] The main reason for converting from initial cyclosporine therapy is the relatively high incidence of cyclosporine nephrotoxicity and its progressive and ultimately irreversible nature.[85] The conversion from cyclosporine use can result in improved renal function and blood pressure control,[71,86,87] and these benefits appear to persist.[87] There can be a major risk of acute rejection and loss of the graft if conversion is undertaken before rejection is carefully excluded, however.[70,88,89] Patients undergoing conversion for refractory rejection have a high risk of graft loss.

Although cyclosporine therapy is undoubtedly effective against cell-mediated acute rejection, its effect on chronic rejection is less certain,[90] and distinguishing chronic rejection from nephrotoxicity may be difficult.

Monoclonal Antibodies

Monoclonal antibody therapy, the most successful example of which is OKT3, became available shortly after cyclosporine was introduced. Polyclonal antilymphocyte antibody preparations (ALG) have had a place in renal transplantation for many years and continue to contribute to immunosuppression protocols.[91] Preparations of ALG, however, have suffered from variation between batches and from side effects associated with their many specificities.[70] Now monoclonal antibodies are being developed that have greater purity, specificity, and reproducible biologic activity. Their use has provided a mechanism for precisely targeting antibody-mediated effects to one cell surface molecule. In renal transplantation this allows immunosuppressive therapy that is more specific than using agents such as azathioprine, steroids, and cyclosporine. On the T-cell surface many antigens provide a target for such specific therapy.[92] Of these, an antibody against CD3 is already in general use, and monoclonal antibodies against the IL-2 receptor and against the T12 molecule have been tested.[93] The potential usefulness of the anti-CD4 antibody has not been overlooked,[94] and efforts are being directed to develop many other monoclonal antibodies for clinical use, including those against activation antigens on T cells.[95] In addition, monoclonal antibodies against cytokines, such as interleukin 2 and interferon gamma, also require assessment as immunosuppressives in renal transplantation.[96] Investigation is also underway into the use of monoclonal antibodies, such as those to passenger leukocytes, to reduce the immunogenicity of grafts.[97]

OKT3 Monoclonal Antibody Therapy

OKT3, a murine monoclonal antibody of the immunoglobulin G2a class, has proved to be a potent immunosuppressive agent owing to its ability to bind the T-cell antigen-receptor complex.[98] The use of OKT3 has been effective as prophylactic therapy in renal transplantation[99,100] and as antirejection therapy,[101-105] but its most appropriate use may be as rescue therapy for steroid-resistant rejection.[106-108] OKT3 therapy has also been shown to benefit patients with predominantly vascular pattern rejection.[109] The recurrence rate of rejection, however, may be unexpectedly high after OKT3 use, as it probably does not eliminate allograft-responding T cells. Its use is thought to result initially in the opsonization and rapid removal of T cells from the circulation. Thereafter, OKT3 appears to rapidly modulate or remove the CD3 or T cell-receptor complex from the surface of T cells, rendering them incapable of activation by antigen recognition.

A number of major problems have emerged with the use of OKT3. A severe febrile reaction and bronchospastic response can follow the administration of the first dose. Pulmonary edema also occurs in patients with fluid overload.[110] The cause of systemic symptoms may be related to the demonstrated ability of OKT3 to activate T cells. This initial T-cell activation, or, alternatively, a wave of T-cell destruction, can result in the release of potent T-cell cytokines leading to systemic effects, including a fall in the glomerular filtration rate.[98,111] Cytokine increases have also been noted with ALG use.[112] After OKT3 use, particularly if high-dose immunosuppressive agents have also been used, a higher incidence of infection may be seen.[107,113,114] Finally, under certain circumstances, T cells with modulated CD3 or T cell-receptor complex may still mediate acute rejection, despite therapeutic levels of OKT3.[115]

An antibody response to OKT3 develops in most treated patients, despite concomitant immunosuppression with cyclosporine or azathioprine. These antibodies may be to the idiotype, isotype, or common determinants of mouse immunoglobulin.[98] Such antibodies may develop during an ini-

tial course, limiting its usefulness and allowing rejection to break through, but they more often develop afterwards, interfering with the use of a second course.[116,117] Reuse can be successful if high-titer anti-OKT3 antibodies have not developed,[118,119] although such reuse is associated with a high incidence of viral infection.[120]

Because anti-idiotypic antibodies developing after OKT3 therapy do not cross-react with all anti-CD3 monoclonal antibodies, using different anti-CD3 monoclonal antibodies may be one approach to reuse.[121] Further, with the use of molecular biologic techniques, human or mouse-human hybrid antibodies can be made that may not stimulate anti-mouse antibody formation.[92] It has been recently suggested that a concurrent infusion of anti-CD4 monoclonal antibody may reduce the formation of recipient anti-OKT3 antibodies by impairing helper T-cell function required for antibody formation.[122]

Anti-Interleukin 2-Receptor Therapy

Interleukin 2 is a critical cytokine involved with the activation, proliferative expansion, and amplification of T cell-mediated rejection responses, such as those occurring with allograft rejection.[123] The IL-2 receptor is expressed mainly on activated T cells, having a low- and high-affinity form, the latter of which binds and internalizes IL-2. In patients undergoing transplantation, the blockade or elimination of T cells expressing the IL-2 receptor can be expected to immunosuppress, in a relatively selective way, the clones responding to an allograft and mediating rejection.[124] The use of anti-IL-2 receptor monoclonal antibodies has proved effective in animal models[125] and has undergone initial trials in humans,[126,127] but not always successfully.[128] This therapy may be synergistic with cyclosporine therapy and is reported to spare suppressor cells.[129]

The initial promise of monoclonal antibody therapy using anti-IL-2 receptors has been enlarged on by the development of a novel IL-2-diphtheria toxin hybrid, which binds to the high-affinity IL-2 receptor on activated cells, mainly T cells, is internalized, and results in cell destruction.[130-132]

Newer Agents

The promise of less nephrotoxic analogues of cyclosporine has not yet been realized.[133] With immunosuppressive characteristics similar to cyclosporine, FK 506 has recently come to increased public attention. Similar to cyclosporine in its ability to inhibit cytokine production,[134-136] FK 506 is currently under investigation for use as a clinical renal transplant immunosuppressive agent, but it has shown considerable hepatotoxicity.[137] Investigation is also proceeding into methods of treating allografts before implantation with agents designed to reduce the ability of grafts to stimulate an immune response.[138,139]

Efforts to Induce Transplant Tolerance

The development of tolerance, or specific unresponsiveness, to donor tissue is the most attractive form of immunosuppression, avoiding drug complications such as infection and malignancy. Anecdotes relate long-term survival of some allografts without the benefit of continued immunosuppressive therapy for prolonged periods.[140] With the establishment of tolerance, immunosuppressive drugs would not be required, and the immune system's natural regulatory mechanism would ensure allograft survival. This ideal is still far from reality in clinical transplantation, although our increased understanding of the mechanisms of such states in animals brings it closer.[141]

In experiments in animals, total lymphoid irradiation and donor bone marrow infusion have been shown to promote a tolerant state, and the role of these agents is being investigated in humans.[142,143] Recent reviews of total lymphoid irradiation in a clinical transplant population found some patients with unresponsiveness to the donor in in vitro immune responses, suggesting that a state of specific donor unresponsiveness may develop in some patients.[144,145] Total lymphoid irradiation is effective immunosuppression, but long-term follow-up shows that patients receiving this therapy have three-year patient and graft survivals, which appear lower than the results of comparable trials using cyclosporine and prednisone.[146]

Clinical Problems in Renal Transplantation

The Diagnosis of Rejection

The diagnosis and treatment of renal dysfunction early in the posttransplant period are difficult but important, because acute tubular necrosis, cyclosporine nephrotoxicity, and acute rejection are hard to distinguish clinically.[147] Percutaneous renal biopsy remains the gold standard for diagnosing the cause of renal transplant impairment, especially with the addition of monoclonal antibody markers to identify infiltrating cells and allograft antigens.[148-151] In particular, the assessment of HLA-DR expression on renal tubular cells may assist in the determination of acute rejection.[152]

Fine-needle aspiration biopsy has become a clinically useful and safe technique for sequentially monitoring graft parenchymal cells and infiltrates.[153] The application of flow cytometric and immunofluorescence technology has added increased usefulness to the technique[154,155]; although the correlation with renal allograft histologic features is good, the information provided about graft structures is more limited.

Renal ultrasonography, radionuclide studies, and magnetic resonance imaging (MRI) may all contribute to the diagnosis of renal transplant dysfunction. Nevertheless, despite their technologic sophistication, none of these methods are sufficient to distinguish among rejection, acute tubular necrosis, and cyclosporine nephrotoxicity. Rejection causes a loss of the corticomedullary demarcation on MRI, but this is not specific.[156-158] Whether MRI is more sensitive than radionuclide studies and sonography has been disputed.[159-161]

Techniques requiring further assessment include duplex Doppler sonography, which may aid in differentiating acute rejection from acute tubular necrosis or cyclosporine nephrotoxicity.[162-164]

Cyclosporine Nephrotoxicity

Cyclosporine nephrotoxicity remains a major problem in renal transplantation, and efforts to resolve whether the immunosuppressive effect of cyclosporine can be separated from its nephrotoxic effect have so far failed.[165] The therapeutic window is so narrow that cyclosporine nephrotoxicity and allograft rejection may coexist. Cyclosporine dosage and cyclosporine serum concentrations may not provide accurate predictors of nephrotoxicity[166-168]; nevertheless, many groups advocate protocols using lower cyclosporine dosages to lessen renal impairment.[169,170]

Cyclosporine can induce nephrotoxicity in both native

and transplanted kidneys,[171] but nephrotoxicity may be worse in kidneys that have had an ischemic insult.[172] Patients receiving cyclosporine have a higher incidence and longer duration of initial graft nonfunction,[71,173] which may result in long-term effects on graft survival.[174] For this reason some centers prefer to use sequential therapy, treating initially with other immunosuppressive agents and introducing a regimen of cyclosporine after graft function has been established.[175] Further, patients with functioning grafts who are receiving long-term cyclosporine therapy generally have a lower glomerular filtration rate than do patients receiving azathioprine and prednisone therapy.[71]

The exact mechanisms of cyclosporine nephrotoxicity are still not known but are under intensive investigation. Cyclosporine causes vasoconstriction of vascular smooth muscle,[176] with an alteration in renal hemodynamics,[177] whereas tubular function is relatively spared.[178] In addition, cyclosporine may be responsible for the arteriolopathy found in some allografts.[179] Cyclosporine may alter the thromboxane-prostacyclin balance, allowing thromboxane-induced vasoconstrictor predominance.[180-183] Certainly cyclosporine use appears to increase thromboxane A_2 levels,[184] and administering thromboxane inhibitors modifies the renal effects of cyclosporine.[185,186] Because cyclosporine is metabolized in the liver through the cytochrome P-450 system, drug interactions may be important in inducing elevated cyclosporine levels predisposing to nephrotoxicity. The use of erythromycin, ketaconazole, steroids, sex hormones, and some calcium channel blockers may induce elevated cyclosporine levels, and rifampin and anticonvulsant therapy may decrease cyclosporine concentrations.[187]

The use of calcium channel blockers may modify cyclosporine nephrotoxicity[188] because cyclosporine binds certain intracellular calcium-binding proteins.[189] Although it is clear that cyclosporine therapy results in lower kidney transplant function than does azathioprine and prednisone therapy,[71] its role in progressive renal impairment is in question.[190] It is best documented that long-term cyclosporine administration may be associated with progressive renal impairment in patients receiving organs other than kidneys,[191,192] where renal transplant rejection does not confuse the issue. In the long term, cyclosporine use is associated with a progressive increase in interstitial fibrosis and tubular and vascular changes.[193] Even when creatinine levels are stable, histologic damage can be detected in the allograft, and stable creatinine levels may be at the cost of increased function in hypertrophied remnant glomeruli.[85,191,194] Thus, the use of serum creatinine levels or even creatinine clearance as an indicator of kidney transplant function may not be sensitive to progressing nephrotoxicity.[195]

Transplant-Associated Hypertension

Hypertension has been a recurrent and persistent problem in renal transplantation.[196] The incidence of posttransplantation hypertension has increased since the widespread use of cyclosporine.[197,198] In association with the impaired lipid profile related to cyclosporine use (reviewed by Chapman and Morris),[84] hypertension may contribute substantially to the death of transplant recipients through the development of arteriovascular and cardiovascular disease.[199,200] Hypertension may also pose a threat to allograft survival.[23,201] The basis of the high incidence of hypertension in renal transplant patients includes factors such as chronic rejection, transplant renal artery stenosis, recurrent renal disease, and increased native-kidney renin production.[202,203] Cyclosporine is a potent inducer of hypertension, in a somewhat different manner from other immunosuppressive agents.[198,204,205] Cyclosporine causes subtle renal impairment,[206] even at normal therapeutic levels,[207] and its use has been associated with sodium retention.[208] The addition of prednisone therapy can also exacerbate hypertension, in part by limiting renal sodium excretion.[209]

Opportunistic Infection

Viral infections have the greatest potential for causing serious infectious complications in kidney transplant recipients. There is also increasing recognition of the role of viruses in triggering posttransplant malignancy, such as lymphoma, hepatoma, Kaposi's sarcoma, and genitourinary cancers.[210,211] Viruses in the herpesvirus group include herpes simplex, herpes zoster, Epstein-Barr virus, and cytomegalovirus (CMV). Cytomegalovirus remains one of the major infectious complications in renal transplantation, where the source of the virus may be the donor organ, blood transfusion, or reactivation of latent virus in the recipient.[212] Cytomegalovirus infections may be deleterious to graft survival and function and may cause substantial patient morbidity and mortality.[213] In most cases primary infections are more severe than reactivation of a latent virus, and both antilymphocyte globulin and OKT3 therapy can potentiate CMV infections.[113,214] It is now recognized that reinfection with a second virus strain may occur in seropositive recipients and that such patients are thus not immune to repeated primary CMV infections.[215] Reserving CMV-negative donors for CMV-negative recipients appears to be a useful preventive measure where practical but may add difficulty to transplant matching.[216-218] Efforts to develop an effective vaccine against CMV have been mostly disappointing,[219-221] but passive immunization with CMV hyperimmune globulin seems effective.[222] Prophylactic therapy with oral acyclovir after transplantation has reduced the incidence of primary CMV infection, and its use may reduce that of Epstein-Barr virus and herpesvirus infection as well as the incidence of Epstein-Barr-related lymphoproliferative disorders.[223] Because rapid diagnosis is critical, new and quicker tests to diagnose CMV infection are being introduced.[224-226] In addition, anti-CMV therapy has recently improved.[227] Whereas CMV lacks the virus-specific thymidine kinase needed for the phosphorylation and activation of acyclovir, newer agents such as ganciclovir are particularly active against CMV.[228-230] Other antiviral agents such as foscarnet[231] are also proving effective. There may be a role for combining therapy with hyperimmune globulin and ganciclovir in high-risk patients with serious infections.[232]

The herpes simplex virus can also be transmitted by the renal allograft,[233] but oral acyclovir has been used with good results to prevent herpes simplex infection in kidney transplant recipients.[234]

Transmission of the human immunodeficiency virus with the transplant organ or blood transfusion can occur despite the screening of donors.[235-237] Diagnosing the acquired immunodeficiency syndrome in persons with transplants may be more difficult, as antibody responses to HIV may be impaired.[238] Patients infected with HIV have a poor prognosis.[239,240] No patient with HIV antibodies should receive or donate an organ.[235] Patients with seroconversion after trans-

plantation should have their immunosuppression reduced, and possibly stopped, but they almost inevitably do poorly.[241]

Malignancy

The increased incidence of malignancy in patients receiving kidney transplants has been well documented[210,242] and is due to immunosuppressive therapy, viral infections, and occasionally to the transmission of cancer with the donor organs.[243] With increasing potency of immunosuppressive medication, the incidence of malignancy in transplant patients has increased.[244]

Skin cancer is the most common manifestation in some countries.[245,246] Epstein-Barr virus-related lymphoma has been of recent concern, and its appearance is associated with potent immunosuppression, especially with multiple drugs and high doses.[78,247,248] Some of these polyclonal lymphoproliferative states are responsive to acyclovir therapy combined with reduced immunosuppression.[249]

Long-term Outcome

The major causes of graft loss in the long term are chronic rejection and patient death. The predominant causes of death are infections, malignant neoplasms, and arteriovascular disease.[210,250,251]

When rejection takes place in long-surviving grafts, it is generally chronic or vascular pattern rejection, although acute rejection can also occur late.[252] Chronic rejection is poorly understood. It generally presents as a slow deterioration in renal function and less often as a sequence of episodes of renal impairment, but both respond poorly to antirejection therapy. Grafts with chronic rejection show progressive pruning of the distal arterial tree. A biopsy specimen shows a vascular pattern of rejection, with fibroblastic endothelial thickening of interlobular and arcuate arteries as well as glomerular and tubular ischemic changes.[253] While conventional theory holds that chronic rejection is predominantly antibody-mediated, evidence is growing that cellular immunity may play an important role.[254]

Chronic rejection is responsible for a significant proportion of late graft losses and contributes to a 3% to 10% annual late graft failure rate.[209,255] Among these losses must be counted grafts rejected because of poor patient compliance,[256,257] which may occur particularly in children and adolescents,[258] sometimes because of changes in appearance induced by therapy.[259,260] Glomerulopathy in kidney transplants may represent rejection, infection,[214] recurrent primary disease, or de novo glomerulonephritis. Some forms of glomerulonephritis, such as focal sclerosing glomerulonephritis,[261] IgA disease,[262] and membranoproliferative glomerulonephritis (type II), have a tendency to recur, often with deleterious consequences, and a proportion of patients go on to lose their grafts.[210,263,264] Immunosuppressive protocols including cyclosporine appear not to be effective in preventing the recurrence of glomerulonephritis in transplanted kidneys.[265]

Future Directions

In the past decade there have been remarkable improvements in the understanding of the mechanisms of rejection and the actions of immunosuppressive agents. In conjunction with better management of infection and better patient care, these factors have been translated into better graft and patient survival after renal transplantation. It is now important to focus on the issues of patient well-being and the level of kidney function.

In the next decade further important advances in renal transplantation should occur, with an array of new immunosuppressive agents, better diagnostic abilities, and better antibiotics. The ability to induce specific transplant tolerance, with a reduction or elimination of the need for nonspecific immunosuppressive agents, has been shown in animal models and needs to be adapted to humans, as suggested by Strober and colleagues.[145] The ability to harness the immune system's own immunoregulatory processes to produce an acquired specific unresponsiveness to organ allografts could well eliminate many of the problems limiting the success of renal transplantation.

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